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10/767,471	01/30/2004	Michele Cargill	CL1505ORD	6499

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,471	CARGILL ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39-46,49-56 and 59-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 39-46, 49-56, 59-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 36, 39-46, 49-56 and 59-73 are pending and examined on the merits.

Applicants have noted (p.7 of Remarks) that the Examiner had indicated claims 36 and 39-45 as allowed in the Advisory Action of 07/11/2008. Claims 36 and 39-45 have been amended with this Request for Continued Examination, and are rejected in this Office Action as detailed below.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/23/2008 has been entered.

This Office Action is in reply to Applicants' correspondence of 06/23/2008.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. New grounds of rejection presented in this Office Action as necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Please note, the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Objections

2. As detailed in the Advisory Action of 05/21/2008, the objections to claims 27, 37, 47, and 57 and to claims 29, 39, 49, and 59, as set forth in the Office Action of

8/10/2007 are **WITHDRAWN** in light of the cancellation of claims the amendments to claims.

Withdrawn Claim Rejection - 35 USC § 112 2nd¶ - Indefiniteness

3. As detailed in the Advisory Action of 05/21/2008, the rejection of claims 1 and 27-45 under 35 U.S.C. 112, second paragraph, as being indefinite as set forth in the Office Action of 8/10/2007, is **WITHDRAWN** in light of the cancellation of claims the amendments to claims.

Withdrawn Claim Rejection - 35 USC § 112 1st - Written Description, New Matter

4. As detailed in the Advisory Action of 05/21/2008, the rejection of claims 1, 29-31, 33-36, 39-46, 39-56, and 59-65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for new matter is **WITHDRAWN** in light of the cancellation of claims the amendments to claims.

Withdrawn Claim Rejection - 35 USC § 112 1st - Written Description

5. As detailed in the Advisory Action of 05/21/2008, the rejection of claims 1 and 27-45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **WITHDRAWN** in light of the cancellation of claims the amendments to claims, as well as the written description training materials revised March 25, 2008, available from www.uspto.gov/web/menu/written.pdf.

New Claim Rejections - 35 USC § 101 - Non statutory subject matter

6. Claims 36, 39, 40, 46, 49, 50, 56, 59, and 60 are rejected under 35 U.S.C. 101 because the claims are directed to non statutory subject matter. The rejected claims are drawn to methods which require only 'determining the identity of a single nucleotide polymorphism' 'as represented by position 101 of SEQ ID NO: 36673' in the nucleic acids of a subject. The methods as claimed do not produce any physical transformation or produce a tangible result. The claims encompass methods requiring only performing mental steps, i.e. determining the presence of a nucleotide variation, by for example, consulting a computer database of sequence information. Thus, the steps of determining the identity of a SNP do not necessarily produce any physical transformation or produce a tangible result.

The claims are all within the statutory category of method claims.

The claims are not within the judicial exception; i.e. they themselves are not laws of nature, natural phenomena or abstract ideas, but they attempt to cover practical applications of a judicial exception. In the rejected claims there is no physical transformation, nor is there a recited practical application that results in a useful, tangible, and concrete result. Since, in the instant claims, there is no step of physical transformation, the Examiner must determine if the instant claims include a useful, concrete, and tangible result. The question is whether the final result achieved by the claimed invention is a result which satisfies all three criteria of being useful, and concrete, and tangible. In determining if the instant claims are useful, tangible, and concrete, the Examiner must determine each standard individually. Furthermore, the

useful, tangible, and concrete result must be either explicitly recited in the claim itself or inherently flow therefrom, rather than merely addressed in the specification.

For an invention to be "useful" it must satisfy the utility requirement of section 101; i.e. it has to be (i) specific, (ii) substantial and (iii) credible. This invention meets the utility requirement.

For a claim to be "concrete," the process must have a result that is reproducible. The claims at issue have results that are reproducible.

For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments. In the instant case, rejected claims do not produce a tangible result. A tangible result requires that the claim must set forth a practical application of the recited computational methods to produce a real-world result. The sole process steps in the claims at issue include "determining the identity", with no real world result recited in the claims. In other words, the outcome of the rejected methods is abstract.

The courts have stated that manipulation of abstract concepts or ideas constitute non-statutory subject matter.

If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. Schrader, 22 F.3d at 294-95, 30 USPQ2d at 1458-59. For example, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process. The instant claims encompass

converting one data set (for example genomic repository data) to another (i.e. a disease risk label) and thus cannot constitute a statutory process.

Therefore the claims are rejected as being non-statutory subject matter.

Maintained and Reinstated Claim Rejection - 35 USC § 112 1st¶ - Scope of Enablement

It is noted that the rejection of claims under 35 USC 112 1st ¶ for encompassing non-enabled scope, which was set forth in the Final Office Action of 08/10/2007 was partially withdrawn in the Advisory Action of 05/21/2008 based on the amendments to the claims of 04/21/2008 which were entered. The instant claims have been amended such that the claims previously indicated as allowable are again rejected under 35 USC 112 1st ¶.

7. Claims 36, 39-46, 49-56 and 59-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for:

> A method for identifying a human individual's risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids;
> detecting the nucleotide content at position 101 of SEQ ID NO: 36,673 or position 101 of the complement of SEQ ID NO: 36,673, in said nucleic acids;
> wherein, detecting the nucleotide T at position 101 of SEQ ID NO: 36,673 , or detecting the nucleotide A at position 101 of the complement of SEQ ID NO: 36,673, identifies the individual as having an increased risk for developing RF+ RA; or wherein detecting the nucleotide C at position 101 of both alleles of SEQ ID NO: 36,673, or detecting the nucleotide G at position 101 of both alleles of the complement of SEQ ID NO: 36,673 identifies the individual as having a decreased risk for developing RF+ RA

does not reasonably provide enablement for identification methods comprising determining the identity of any SNP that is 'represented by' position 101 of SEQ ID NO: 36,673, as recited in the rejected claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for identifying an individual who has an altered risk for developing RF+ RA.

The claims encompass determining the identity of any nucleotide content that is represented by position 101 of SEQ ID NO: 36,673, where the specification offers no limitations as to what is required for any nucleotide content to be 'represented by' position 101 of SEQ ID NO: 36,673.

The nature of the inventions requires knowledge of an association between the broadly claimed nucleic acid content and altered risk of having RF+ RA.

Direction provided by the specification and working example

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.25).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 36,673, which may be either a C or

a T, and is also identified as hCV16021387 and known in the art as rs2476601. The specification teaches that the frequency of the particular allele was analyzed in two (p.119 lns.6-20) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that various strata (e.g. stratification by sex, age of RA onset, RF+, and number of high or low risk HLA epitopes (p.21)) of each population was also analyzed.

The specification teaches the specific association of the T allele (i.e. a T nucleotide a position 101 of SEQ ID NO: 36,673) with an increased risk of RA as the T allele is found at a significantly higher frequency in the case samples of the Discovery Set and the Replication Set (Table 6; p.121, lns.21-27). It is noted that Table 6 designates the 'A' allele as associated with the increased risk of RA, and the specification indicates that nucleotide content may be described as the reverse complement of the nucleotide content at the position (e.g. p.19, lns.13-19), thus the A allele of the reverse complement of SEQ ID NO: 36,673 is the T allele of SEQ ID NO: 36,673. The specification does not provide any genotype analysis, and as such it is possible only to conclude that the T allele in either the T/T or C/T genotype is indicative of increased risk of RF+-RA, and C/C genotype is indicative of decreased risk of RF+ RA. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+. While the instant specification provides that the T allele is indicative of increased risk for RA in the Replication Set, and specifically for the RF+ stratum, the instant specification provides

no data for the RF- stratum of the replication set, nor any indication as to how many individuals in the Replication Set were either RF+ or RF-. Thus while the data of specification teaches an association of the T allele with RF+ RA, it is not clear from the specification if the T allele is associated with RF- RA.

The instant specification asserts that since autoimmune diseases share certain similar features that may be due to common genetic factors, SNPs associated with RA may also be used as makers for other autoimmune diseases (p.9, ln.1; p.121, ln.28). However, the instant specification provides no indication of any particular level of association of any SNP with any phenotype other than RA.

The instant specification provides only the association analysis of either C or T content at position 101 of SEQ ID NO: 36,673, and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 36,673.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in SEQ ID NO: 36,673 and altered risk for developing RF+ RA. And because the claims encompass determining the identity of any SNP that is 'represented by' position 101 of SEQ ID NO: 36,673, it is relevant to point out the unpredictability in associating any

particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). The unpredictability as demonstrated by Hacker et al is particularly relevant considering that neither the instant specification, nor any art recognized terminology, provide any limitations regarding what is needed for any polymorphic content to be 'represented by position 101 of SEQ ID NO: 36,673'.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would include determining the association of any polymorphic content (any substitution, insertion, or deletion) in any sequence context that may be considered to be 'represented by position 101 of SEQ ID NO: 36,673' with an altered risk (increased risk or decreased risk) of developing RF+ RA. This would involve large case:control studies in multiple human populations, and the analysis of different sequence variants. Even if such a large analysis were to be performed, there is no guarantee that one would find any significant associations beyond those specifically taught in the particular example of the instant specification.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its

high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have argued (p.7-8 of Remarks) that the claims have been amended to require the nucelotide:phenotype association that has been indicated as enabled by the instant specification. In the instant case, the Examiner has indicated that the claims are enabled in so far as they required the detection of the particular nucleotide content at position 101 of SEQ ID NO: 36,673. However, as detailed in the rejection, the claims have been amended to encompass 'determining the identity of a single nucleotide polymorphism (SNP) in said human's nucleic acids as represented by position 101 of SEQ ID NO: 36,673'. The language of 'as represented by position 101 of SEQ ID NO: 36,673' is not limited by any teachings or definition in the instant specification, and is not limited by any terminology that is typically recognized in the art. Thus the claim language encompasses the determination of SNPs other the particular elected SNP of the instant invention as described in the examples of the specification. For instance a different SNP may be considered to be 'represented by' the elected SNP if the different SNP has C/T polymorphic content in any sequence context, or is in a sequence encoding a homologous protein, is in a similar codon or similar intronic position.

The rejection as set forth is **MAINTAINED**.

Conclusion

8. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Art Unit 1634